A top priority in pre-eclampsia research

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A top priority in pre-eclampsia research: development of a reliable and inexpensive urinary screening test

Pre-eclampsia is a leading cause of maternal and perinatal mortality and morbidity worldwide, with an estimated 60 000 pre-eclampsia-related maternal deaths per year.[1] This complication of human pregnancy has increased in incidence in the past decade and can be avoided by timely and effective care (secondary prevention).[2] Pre-eclampsia is defined by new hypertension and organ damage (mainly involving the kidney and sometimes the liver) that can evolve into eclamptic seizures, maternal stroke, and abruptio placentae. Despite extensive research by obstetricians, paediatricians, immunologists, cardiologists, epidemiologists, and anthropologists, pre-eclampsia remains a complex and heterogenous disorder of elusive pathophysiology.

We formed the International Group of Reproductive Immunology, Immunological Tolerance and Immunology of Preeclampsia in 1998, aiming to study the causes and address key gaps in the knowledge of pre-eclampsia. Our consensus is that the condition arises because of altered placental development as demonstrated by impaired secretion of pro-angiogenic placental growth factor (PlGF), which leads to placental release into the maternal circulation of angiogenic factors, including soluble endoglin (sEng) and soluble fms-like tyrosine kinase (sFlt). These factors are strongly correlated with development of maternal syndrome (hypertension, proteinuria, and organ damage) and are shown to increase at or before onset of clinical symptoms.[3,4]

In *The Lancet*, Emmanuel Bujold and colleagues[5] commented on a controlled trial from the PARROT group describing testing of pro-angiogenic placental growth factor to optimise pre-eclampsia diagnosis.[4] Bujold and colleagues[5] highlighted that this test was used in large, high-resource maternity units; however, the investigators suggested to evaluate the additional role of ultrasound in future research to improve clinical outcomes. Since the highest incidence of pre-eclampsia occurs in low-income and middle-income countries that rely on basic means,[1] it would be most appropriate to focus on developing an inexpensive, easy-to-administer (with minimal discomfort), reliable, and validated test. On the basis of research progress to date, several research priorities were agreed during a workshop on Reunion Island, France, in December 2018, which involved 22 participants recruited from research groups worldwide. The first and paramount priority is to achieve a reliable and inexpensive screening test, which represents the main issue to be addressed: optimising clinical assistance to prevent maternal and fetal morbidity. Urinary tests remain the best inexpensive option that could be administered in low-resource settings and even rural areas in low-income countries. Therefore, patients might be identified and referred to specific clinical pathways offering increased surveillance to avoid medical interventions being ineffective because of late presentation.

Various candidate biomarkers and approaches exist, but the most exciting and tractable options as urinary tests are detection of urinary misfolded proteins using azo-dye Congo Red,[6] adipsin,[7] and inositol phosphoglycans P-type.[8] Kara Rood and colleagues[6] did a prospective study in a university setting in Ohio, USA, using a semi-quantitative analysis based on a specifically developed paper-based urine test kit. Urinary adipsin is another valid candidate that showed high sensitivity (90%) and good specificity (78%) in a longitudinal study in a university hospital in China.[7] Like the PARROT study,[4] these two studies focused on the potential of the test to optimise diagnosis, whereas screening potential was minimally investigated. A longitudinal study in a low-income country[9] also identified inositol phosphoglycans P-type as one of several metabolic molecules in maternal urine that show identification of women destined to develop pre-eclampsia 3–4 weeks before onset of clinical symptoms is possible. Other emerging urine biomarkers that showed positive performances are neutrophil gelatinase-associated lipocalin and complement biomarkers, such as C5a and C5b-9.[10] Detection and quantification of inositol phosphoglycans P-type, neutrophil gelatinase-associated lipocalin, and complement biomarkers are achieved via ELISA; therefore, development of a simple method on the basis of urine strips or similar should be feasible. Clinical studies including urinary routine testing during every antenatal visit would test improvement of early diagnosis compared with routine antenatal care and capacity for tertiary prevention.[2] Given the availability

of several candidate urinary biomarkers, we propose that diagnostic companies should allocate resources towards development of a low-cost urine test that is specific for pre-eclampsia diagnosis, as this test would have substantial benefits, particularly in low-income and middle-income countries where resources for expensive blood tests might not be available.

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TWR reports being a co-author on inositol phosphoglycans pre-eclampsia publications while on the University College London Medical School board. TWR was a coinventor on an InositolPhospho Glycan pre-eclampsia diagnostic patent, which has now lapsed. TWR provides laboratory reagents to academic groups for pre-eclampsia clinical trials. SAK reports consultancy work for Roche and Thermofisher and receiving a research grant from Siemens during the writing of this Comment; being a founder and advisory board member of Aggamin Pharmaceuticals outside the submitted work; Preeclampsia Biomarker patents with royalties paid to Beth Israel Deaconess Medical Center; and being a member of the Scientific Advisory Board for the Pre-eclampsia Foundation. All other authors declare no competing interests.

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